TABLE OF CONTENTS

I. BACKGROUND

Guidance document for clinical development programs for products for the treatment of rheumatoid arthritis (RA)

In the document entitled "Guidance for Industry: Clinical Development Programs for Drugs, Devices, and Biological Products for the Treatment of Rheumatoid Arthritis (RA)," the FDA offers guidance on the conduct of clinical trials in RA. The document describes six claims: Reduction in the signs and symptoms of RA; Major clinical response; Complete clinical response; Remission; and Improvement in physical function/disability. To support the claim of reduction in signs and symptoms, a clinical trial should be at least six months' duration unless the product belongs to an already well-characterized pharmacologic class (e.g. NSAIDs). Acceptable outcome measures include validated composite endpoints of signs and symptoms as well as well-accepted sets of signs and symptoms measures. Evidence should be provided about symptoms over time during the trial and not just at the final study visit.

The RA guidance document also discusses the importance of assessing the use of new products in combination with concurrent active therapies including corticosteroids and NSAIDs. In particular, because methotrexate is used to treat many patients with RA, the potential for immunosuppression from combination therapy should be assessed.

International Conference on Harmonisation guideline on assessment of clinical safety

Document E1A of the International Conference on Harmonisation, entitled "Guideline on extent of population exposure required to assess clinical safety for drugs," recommends levels of exposure for therapeutic agents intended for long-term use in non-life threatening conditions. The document states that to adequately characterize the expected adverse event profile, experience should be available from 300-600 patients treated for 6 months, 100 patients treated for a minimum of one year and a total number of 1500 individuals exposed at all, including short-term exposure.

Proposed indication by sponsor

ENBREL is indicated for the treatment of patients with active rheumatoid arthritis.

II. PIVOTAL TRIAL DESIGN AND CONDUCT

ENBREL was developed for the treatment of active rheumatoid arthritis (RA). It is proposed to be used either alone or in combination with methotrexate. Immunex submitted a Biological License Application (BLA) on May 7, 1998, containing information about the origin and manufacturing of ENBREL, pre-clinical data, and an analysis of clinical data for safety and efficacy.

The results of three randomized controlled trials were submitted (table 1). Trial 16.0009, a phase 3 pivotal trial, will be discussed in this section. The two additional trials: 16.0004, a phase 2 trial, and 16.0014, a phase 2/3 methotrexate combination trial are presented in section IV below.

Table 1: Controlled studies completed in RA

Protocol #	Location	Design Patient Population	Study Drug(s) Doses	No. of subjects	Duration of Treatment
• 16.0009	USA Canada	• Double-blind, randomized, parallel, placebo-controlled, Phase III • DMARD-failing active RA	SC 2x/wk • TNFR:Fc (mg) 10 25 • Placebo	234	26 wks
• 16.0004	USA	• Double-blind, randomized, placebo-controlled, parallel, Phase II • Active RA	SC 2x/wk • TNFR: Fc (mg/m^2) 0.25 2 16 • Placebo	180	12 wks
• 16.0014	USA	• Double-blind, randomized, placebo-controlled, randomized, parallel, Phase II/III • Active RA receiving methotrexate: 12.5 to 25 mg PO 1x/wk	SC 2x/wk • TNFR:Fc (mg) 25 • Placebo	89	24 wks

A. Pivotal study design

Study 16.0009 was a double-blind, placebo-controlled, phase 3 trial in subjects with active RA randomized to receive 10 or 25 mg ENBREL or placebo subcutaneously twice weekly for six months. The two doses were chosen because of results from an earlier phase 2 study. The study was carried out in 16 sites (15 in the US, 1 in Canada). The study specified the following inclusion criteria:

- Meet 1987 ARA criteria for RA

- Failed therapy with at least one but not more than four DMARDs (hydroxychloroquine, oral or injectable gold, methotrexate (MTX), azathioprine, D-penicillamine, sulfasalazine). Failure was defined as discontinuation of therapy because of lack of efficacy (LOE) as determined by the Principal Investigator.
- Active RA at the time of enrollment including ≥10 swollen joints and ≥12 tender/painful joints and at least one of: ESR ≥28 mm/hr, CRP >2.0 mg/dL, duration of morning stiffness ≥45 min.
- RA functional status of Class I, II, or III
- At least 18 years of age.

The trial excluded subjects who had:

- Previous receipt of TNFR:Fc or investigational drugs or biologics
- Receipt of intra-articular corticosteroids within 4 weeks of enrollment
- Receipt of DMARDs (e.g., hydroxychloroquine, oral or injectable gold, MTX, azathioprine, D-penicillamine, or sulfasalazine) within 4 weeks of study drug administration.
- Receipt of cyclophosphamide or cyclosporine in the 6 months prior to study drug administration.

The trial allowed the use of stable doses of NSAIDs and doses of oral corticosteroids up to the equivalent of 10 mg/d of prednisone as well as certain other pain medications (see appendix table 1 for the list of allowed concomitant medications).

The protocol allowed for early escape for subjects who believed they were not benefiting from their assigned therapy if they met the following protocol-prespecified conditions for lack of efficacy:

- At least 2 wks on drug with inadequate control
- No improvement in physician/patient global or a worsening
- <10% improvement in tender joint count (TJC), swollen joint count (SJC) or a 20% worsening
- TJC>12 and SJC>10
- The subjects condition necessitates a change in anti-rheumatic therapy

Primary efficacy endpoint

The primary efficacy endpoint of the trial was the proportion of subjects achieving a 20% ACR response rate at 3 months (see appendix table 2 for criteria for a 20% ACR response). Subjects who discontinued study drug due to toxicity were considered to be non-responders with respect to the primary endpoint regardless of their level of clinical response. In addition, subjects who chose to discontinue study medication because of lack

of efficacy were considered non-responders if they met the following protocol-defined criteria:

- Symptoms were not adequately controlled during at least a 2 week trial of study drug;
- No improvement in physician/patient global assessment over baseline OR an increase in physician/patient global assessment by more than two points compared to the best global assessment in the study;
- Patient either had (a) ≥20% worsening in either the total tender joint count or the total swollen joint count compared to the best joint evaluation, or (2) ≤10% improvement in the total tender joint count or the total swollen joint count compared to baseline;
- A total tender joint count ≥12 and total swollen joint count ≥10;
- Rheumatic symptoms necessitated a change in antirheumatic therapy (i.e., DMARDs or corticosteroids)

Assuming a response rate of ≤ 25% in the placebo group and ≥ 50% in the 25 mg group, estimated from the results of the phase 2 study, the sample size of 75 patients per group afforded 86% power to detect a significant difference between treatments using a two-sided, alpha = 0.05 level test. To minimize bias due to unblinding, an independent, blinded joint assessor carried out the joint assessments. The blinded joint assessor was not involved in the care of patients and was asked not to discuss disease activity or the treatment with patients or the Principal Investigator. The previous two injection sites were covered up during joint assessments.

B. Study conduct

Study drug and placebo preparations.

ENBREL was supplied as a sterile lyophilized powder in vials containing 10 mg or 25 mg ENBREL in ———————— with mannitol and sucrose. Placebo was supplied as a sterile lyophilized powder in vials containing the same ———————— , mannitol and sucrose.

Randomization

Patients were assigned to one of three treatment groups according to a computer-generated randomization schedule with blocked randomization using a block size of three. Randomization was stratified according to study site and equal allocation of treatments.

For the first 116 patients, subjects were randomized at the time the consent form was signed. This process was changed because 12 patients discontinued after randomization but prior to study drug administration when they did not meet study eligibility criteria. With the enrollment of the 117th patient, subjects were randomized after all laboratory

screening test results were received and the patient was deemed eligible (approximately 5 days prior to study drug administration).

C. Patient population

Phase 3 study: Patient disposition

A total of 246 patients were randomized to receive placebo (83 subjects), ENBREL 10 mg (82 subjects) and ENBREL 25 mg (81 subjects) (table 2). The twelve subjects who never received study drug were distributed in a balanced manner between the various study arms. The remaining 234 subjects comprise the modified intent-to-treat population of subjects who received at least one dose of study agent, as specified in the protocol. Fewer subjects completed 12 weeks of dosing in the placebo arm (38/80 subjects, 52%) compared to the 10 mg arm (61/76, 80%) or the 25 mg arm (66/78, 85%). The major reason that subjects did not complete 12 weeks of dosing in the placebo arm was lack of efficacy by protocol-specified criteria as seen in 35/80 subjects compared to 9/76 and 8/78 subjects in the 10 mg and 25 mg arms, respectively. FDA review of the information for the placebo subjects who discontinued study agent due to lack of efficacy confirmed that these subjects met protocol-specified criteria. The other reasons for subjects discontinuing study medication before 12 weeks include not the meeting protocol-specified criteria for lack of efficacy, protocol violations, adverse events and loss to follow-up. No imbalances were noted between study arms in these other reasons for discontinuing study medication before 12 weeks.

Fewer subjects completed 26 weeks of dosing in the placebo arm (27/80 subjects, 34%) compared to the 10 mg arm (54/76 subjects, 71%) or the 25 mg arm (60/78 subjects, 77%). The reasons for discontinuing study medication between 12 weeks and 26 weeks were the same as for discontinuation before 12 weeks. Discontinuation for lack of efficacy per protocol-specified criteria was more common in the placebo subjects compared to the two ENBREL-treated arms while other reasons for reasons for discontinuation were similar between the various arms.

Table 2: PATIENT DISPOSITION

Patients entered 246		
PLACEBO	**ENBREL 10 MG**	**ENBREL 25 MG**
Patients randomized **83**	Patients randomized **82**	Patients randomized **81**
Received at least one dose (ITT analysis population) **80 (96%)**	Received at least one dose (ITT analysis population) **76 (93%)**	Received at least one dose (ITT analysis population) **78 (96%)**
Completed 12 weeks dosing **38 (48%)**	Completed 12 weeks dosing **61 (80%)**	Completed 12 weeks dosing **66 (85%)**
• LOE per protocol: **35** • Other LOE:**2** • Protocol violations: **3** • AE: **1** • Lost to follow-up: **1**	• LOE per protocol: **9** • Other LOE: **2** • Protocol violations: **1** • AE: **3** • Lost to follow-up: **0**	• LOE per protocol: **8** • Other LOE: **0** • Protocol violations: **1** • AE: **3** • Lost to follow-up: **0**
Completed 26 weeks dosing **27 (34%)**	Completed 26 weeks dosing **54 (71%)**	Completed 26 weeks dosing **60 (77%)**
• LOE per protocol: **7** • Other LOE:**1** • Protocol violations: **0** • AE: **2** • Lost to follow-up: **0**	• LOE per protocol: **5** • Other LOE: **0** • Protocol violations: **1** • AE: **1** • Lost to follow-up: **0**	• LOE per protocol: **4** • Other LOE: **0** • Protocol violations: **2** • AE: **0** • Lost to follow-up: **1**

The demographics of the study subjects in given is table 3. The large majority of the subjects were female and Caucasian as expected based on the known epidemiological features of RA. The subjects had a long prior history of RA and the vast majority were RF^+. Most subjects had received a mean of approximately 3 prior DMARDs, including MTX in approximately 90%. Subjects in the various arms were balanced for most parameters with the exception of concomitant use of corticosteroids which was more common in the 25 mg arm than the other two arms and concomitant use of NSAIDs which was more common in placebo subjects than in either of the active treatment arms.

Table 3: Demographics of phase 3 study

(modified ITT population)

	Placebo		TNFR:Fc	
Characteristic ITT	N = 80		10 mg N = 76	25 mg N = 78
Mean age (years)	51		53	53
Female (%)	76		84	74
Caucasian (%)	89		96	94
Mean weight (kg)	73		73	77
Mean RA duration (years)	12		13	11
Rheumatoid factor positive (%)	78		80	78
Previous MTX (%)	90		92	87
Mean no. prior DMARDs	3.0		3.4	3.3
DMARDs (any) at washout (%)	48		46	45
MTX at washout (%)	26		18	21
hydroxychloroquine at washout (%)	26		20	21
Concomitant therapy at baseline (%)				
corticosteroids	58		66	81*
NSAIDs	84		67*	67*
* $p < 0.02$; each TNFR:Fc group vs. placebo (p-values determined by likelihood ratio chi-square test)				

Subjects in all three arms had high levels of arthritis activity at baseline as measured by tender joint counts, swollen joint counts, physician and patient global assessment, morning stiffness, pain, quality of life and acute phase reactants as indicated in table 4. No major imbalances were evident in the levels of arthritis activity between the various treatment arms.

Table 4: Baseline arthritis activity measures

	Total group at baseline (N)		
Measure	PL (80)	10 mg (76)	25 mg (78)
Tender joint count (Scale 0 - 71)	35	34	33
Swollen joint count (Scale 0 - 68)	25	25	25
Physician global assess (0 = best, 10 = worst)	7	7	7
Patient global assess (0 = best, 10 = worst)	7	7	7
Morning stiffness (hr)	5	4	5
Pain (VAS) (0 = best, 10 = worst)	7	7	7
Quality of life (HAQ) (0 = best, 3 = worst)	1.7	1.7	1.6
ESR (Normal range: 1 - 13 mm/hr for men and 1 - 30 mm/hr for women)	39	44	35
CRP (Normal range: 0 - 0.79 mg/dL)	4	5	5

III. PIVOTAL TRIAL: EFFICACY ANALYSIS

A. Primary endpoint

Results on analyses of the primary and secondary endpoints are summarized in table 5.

Table 5: Primary and secondary endpoints
Proportion of subjects meeting ACR response criteria

	Placebo	TNFR:Fc	
Time	N = 80 n (%)	10 mg N = 76 n (%)	25 mg N = 78 n (%)
ACR 20%			
Month 3	18 (23)	34 (45)*	48 (62)*†
Month 6	9 (11)	39 (51)*	46 (59)*
ACR 50%			
Month 3	6 (8)	10 (13)	32 (41)*†
Month 6	4 (5)	18 (24)*	31 (40)*†

*$p \leq 0.003$, each vs. placebo by likelihood ratio chi-square
†$p < 0.05$, 10 vs 25 mg

A statistically significant increase in the proportion of subjects who achieved an ACR 20 response at month 3 was observed in the subjects receiving ENBREL 25 mg (48/78, 62%) or ENBREL 10 mg (34/76, 45%) compared to those who received placebo (18/80, 23%). A significant increase in the proportion of subjects achieving an ACR 20 response was also observed at month 6. More subjects in the ENBREL 25 mg arm achieved the more substantial ACR 50% response both at month 3 and month 6 compared to placebo. While more subjects achieved an ACR 50% response in the ENBREL 10 mg arm at 6 months compared to placebo, the difference at 3 months did not reach statistical significance.

Patients who received 25mg of ENBREL compared to 10mg of ENBREL were more likely to achieve an ACR 20 response at month 3. However, at month 6, the differences between the proportion of subjects with an ACR 20 response in each dose arm were not significant. In contrast, when the ACR 50% response is considered, an increase in the proportion of subjects attaining this more substantial level of response was observed in the subjects who received the higher dose of ENBREL both at month 3 and month 6.

To further assess the primary endpoint, the FDA conducted an additional statistical test using the Smirnov Test (table 6). In this analysis, subjects are grouped in the following categories: those who did not attain an ACR20; those who attained a 20% but not a 50% response; those who attained a 50% but not a 70% response; those who attained a 70% or greater response. This test assesses the difference between the level of clinical response attained and not just whether the subject did or did not achieve a particular level of

response. The Smirnov Test does not rely on the data fitting a normal distribution or any other assumed distribution. The results of this analysis are that the 25 mg arm was associated with higher levels of response compared to both placebo and the 10 mg dose. The results were highly statistically significant.

Table 6: FDA analysis of primary endpoint by Smirnov Test

Efficacy: Phase III Study 16.0009, Month 3 (all randomized subjects)					
	No ACR20	ACR20	ACR50	ACR70	Total
Placebo	65 (78%)	12 (14%)	3 (4%)	3 (4%)	83
10 mg	48 (59%)	24 (29%)	4 (5%)	6 (7%)	82
25 mg	33 (41%)	16 (20%)	20 (25%)	12 (15%)	81
Total	146 (59%)	52 (21%)	27 (11%)	21 (9%)	246

Placebo vs. 25 mg: p=0.0000 (two-sided exact conditional Smirnov test)
10 mg vs 25 mg: p=0.0006 (two-sided exact conditional Smirnov test)
p=0.0004 (one-sided exact conditional Smirnov test)

B. Corroborating analyses

The results of the sponsor's analysis of the individual components of the ACR index in the various treatment arms are shown in table 7. Last Observation Carried Forward (LOCF) was used to impute missing data for the timepoints after subjects discontinued study medication for lack of efficacy or for other reasons. Subjects treated with ENBREL at either dose level exhibit a statistically significant improvement in each of the components of the ACR index, including the objective components, the ESR and CRP.

Table 7: Components of ACR response index
(median % improvement compared to baseline)

	Placebo	TNFR:Fc	
Parameter	N = 80	10 mg N = 76	25 mg N = 78
No. of tender joints	7	42*	66*
No. of swollen joints	4	36*	53*
VAS	4	46*	56*
Physician global assessment	0	43*	50*
Patient global assessment	0	39*	50*
ESR	0	23*	40*
CRP	-28	50*	50*
Duration of morning stiffness	18	68*	83*

* $p < 0.05$, each TNFR:Fc group vs. placebo, by ANOVA except CRP and duration of morning stiffness which were calculated by Kruskal-Wallis test

To corroborate the primary endpoint, the sponsor analyzed the ability of ENBREL to normalize the results of abnormal laboratory parameters. As shown in table 8, treatment with ENBREL 25 mg was associated with a significant increase in the proportion of subjects with normalization of CRP, ESR, platelet count, WBC count, albumin. More subjects treated with ENBREL 25 mg had normalization of hemoglobin as well, but the results were not statistically significant.

Table 8: Normalization of Objective Laboratory Measures

Laboratory Parameter	Placebo N = 80 n(%)	TNFR:Fc 10mg N = 76 n(%)	TNFR:Fc 25mg N = 78 n(%)
CRP			
Mean value BL (mg/dL)	4.1	5.3	4.7
No. (%) pts. with nl value			
BL	17 (21)	13 (17)	16 (21)
last value	14 (18)	20 (26)	36 (46)*
ESR			
Mean value BL (mm/hr)	39	44	35
No. (%) pts. with nl value			
BL	34 (43)	24 (32)	39 (50)
last value	27 (34)	40 (53)*	52 (67)*
Hemoglobin			
Mean value BL (g/dL)	13.0	12.7	13.3
No. (%) pts. with nl value			
BL	59 (78)	55 (73)	65 (84)
last value	57 (75)	60 (80)	67 (87)
Platelet count			
Mean value BL (/μL)	360	358	358
No. (%) pts. with nl value			
BL	51 (68)	49 (65)	54 (70)
last value	52 (69)	60 (80)*	65 (84)*
White blood cell count			
Mean value BL (cells/μL)	8.7	9.3	10.2
No. (%) pts. with nl value			
BL	57 (75)	51 (68)	46 (60)
last value	50 (66)	51 (68)	59 (77)*
Albumin			
Mean value BL (g/dL)	3.7	3.6	3.6
No. (%) pts. with nl value			
BL	64 (82)	58 (77)	58 (75)
last value	65 (83)	67 (89)*	70 (91)*

* $p < 0.05$ for within treatment group change
(p-values determined by Stuart-Maxwell chi-square test)

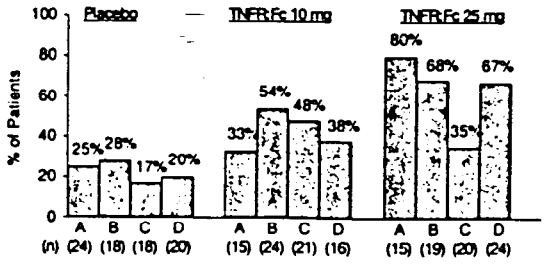
Subset analyses for the primary efficacy endpoint.

To assess the influence of baseline variables on the results of the study, the FDA carried out a logistical regression analysis (appendix table 3). Of the baseline variables analyzed, age, body surface area, weight, height, baseline RF-positivity, and study site were not predictive of a subject's likelihood of having an ACR 20 response. In contrast, a higher tender joint count and a higher swollen joint count were weakly predictive of have an ACR 20 response. Baseline HAQ was inversely associated with the likelihood of having an ACR 20 response, that is subjects with high scores on the HAQ were somewhat less likely to respond with an odds ratio of 1.8. However, even accounting for HAQ scores, assignment to the ENBREL 25 mg treatment arm was the most highly predictive variable with an odds ratio of 2.7.

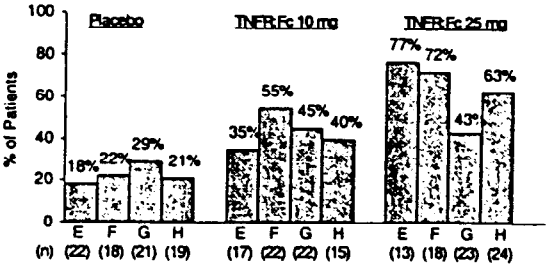
Since fixed doses of drug were used in the trial, smaller subjects received relatively higher doses on a weight-adjusted basis. To assess the importance of body size in predicting clinical responses, the proportion of ACR 20 responders was assessed in subjects subdivided by size based on body surface area and weight. There was no evidence for a lower response rate in the larger subjects (figure 1).

Figure 1: Responses by body surface area (BSA) and by weight

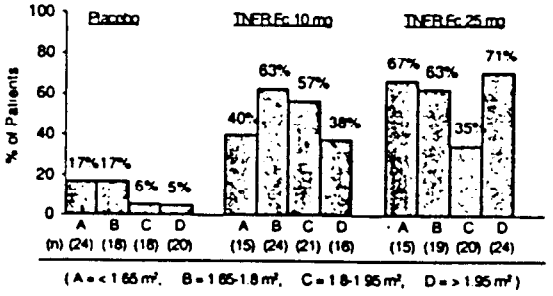
20% ACR Response at 3 Months by BSA



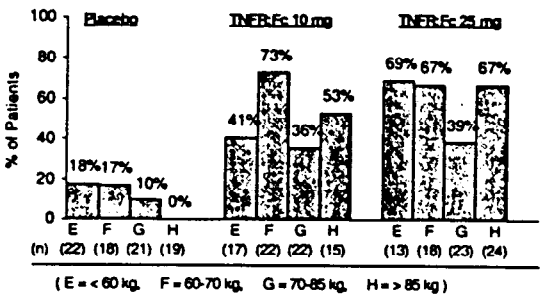
20% ACR Response at 3 Months by Weight



20% ACR Response at 6 Months by BSA



20% ACR Response at 6 Months by Weight



Analysis of baseline demographic features had revealed an imbalance between study arms in the proportion of subjects who were receiving concomitant steroids and NSAIDs. As shown in table 9, response rates were similar in the various treatment arms for subjects who were receiving concomitant corticosteroids as for those who were not. Similar results are shown in table 10 for subjects who were or were not receiving concomitant NSAIDs.

Table 9: Response rate by corticosteroid use

	Placebo	TNFR:Fc	
		10 mg	25 mg
Parameter	n (%)	n (%)	n (%)
20% ACR			
Month 3			
Corticosteroids	10/46 (22)	23/50 (46)	38/63 (60)
No corticosteroids	8/34 (24)	11/26 (42)	10/15 (67)

Table 10: Response rate by NSAID use

	Placebo	TNFR:Fc	
		10 mg	25 mg
Parameter	n (%)	n (%)	n (%)
20% ACR			
Month 3			
NSAIDs	14/67 (21)	26/51 (51)	34/52 (65)
No NSAIDs	4/13 (31)	8/25 (32)	14/26 (54)

Analyses were carried out to determine whether clinical efficacy could be demonstrated in a variety of different patient subsets. A higher proportion of ACR 20 responses were seen for the ENBREL 25 mg-treated subjects compared to placebo in both male and female subjects (table 11), in subjects older than 64 years of age as well as subjects under 64 years of age (table 12). Too few non-Caucasians were treated to reach conclusions about the rate of ACR 20 responses. The response rate analyzed by ethnicity is presented in table 13 for the three randomized controlled trials of ENBREL.

Table 11: Response rate by gender: phase 3 trial

20% ACR Response at 3 Months by Gender

	Placebo	25 mg
Parameter	N = 80 n (%)	N = 78 n (%)
Male	4/19 (21)	11/20 (55)
Female	14/61 (23)	37/58 (64)

Table 12: Response rate by age

20% ACR Response at 3 Months by Age

	Protocol 16.0009	
	Placebo	25 mg
	N = 80	N = 78
Age	n (%)	n (%)
18 - 64	15/67 (22)	40/62 (65)
≥ 65	3/13 (23)	8/16 (50)

Table 13: Response rates by ethnicity

20% ACR Response at 3 Months by Ethnicity

	Protocol 16.0004		Protocol 16.0009		Protocol 16.0014	
	Placebo	TNFR:Fc	Placebo	TNFR:Fc	Placebo/MTX	TNFR:Fc/MTX
		16 mg/m²		25 mg		25 mg
	N = 44	N = 44	N = 80	N = 78	N = 30	N = 59
Race	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Caucasian	5/40 (13)	30/41 (73)	16/71 (23)	46/73 (63)	7/25 (28)	30/45 (67)
Non-Caucasian	1/4 (25)	3/3 (100)	2/9 (22)	2/5 (40)	3/5 (60)	9/14 (64)

When the results of the pivotal trial are analyzed based on the duration of disease, similar rates of response were seen with ENBREL treatment among subjects with disease of recent onset as well as subjects with long-standing RA (table 14).

Table 14:Response rate by duration of disease: 16.009

Disease duration	Placebo	10 mg	25 mg
0-5 yrs	7/22 (32%)	8/15 (53%)	14/21 (67%)
6-10 yrs	4/21 (19%)	8/15 (53%)	11/20 (55%
> 10 yrs	7/37 (19%)	18/46 (39%)	26/37 (70%)

A linear regression analysis performed by the sponsor identified baseline rheumatoid factor positivity or negativity as a predictive factor for responses with ENBREL treatment. The

proportion of responders in the various treatment groups grouped by RF status at baseline is presented in table 15. It can be seen that for ENBREL 25 mg-treated subjects, the proportion of responders in the RF-negative patients is lower than in the RF-positive group. However, the numbers of RF-negative subjects in the trial was small. In addition, high levels of clinical responses were observed among some subjects who were RF-negative. An FDA analysis showed that of 17 ENBREL 25 mg-treated subjects with a RF titer below 20, there were 5 responders: 3 subjects had an ACR response between 50% and 70% and 2 subjects had an ACR response exceeding 70%. In contrast, among 15 placebo-treated subjects with a RF titer below 20, there were 5 responders: 4 with a response between 20% and 50% and one with a response exceeding 70%.

Table 15: Response rate by RF status

	Placebo	TNFR:Fc	
Parameter	n (%)	10 mg n (%)	25 mg n (%)
20% ACR			
Month 3			
RF positive	10/62 (16)	27/61 (44)	41/61 (67)
RF negative	7/16 (43)	6/13 (46)	6/16 (38)
Month 6			
RF positive	2/62 (3)	31/61 (51)	40/61 (66)
RF negative	6/16 (38)	7/13 (54)	5/16 (31)

C. Other analyses

Sensitivity analysis

If unblinding of study subjects had occurred during the pivotal trial, an unbalanced pattern of discontinuation of study agent could have biased the study results in favor of ENBREL. Unblinding side effects, like injection site reactions and URIs (see below), might unblind subjects and investigators to whether the subject is receiving placebo or active agent and possibly introduce bias into the trial. In contrast, there exists no obvious evidence of unblinding between the 10 mg and 25 mg dose arms because:

a) potentially unblinding side effects were of similar incidence between the 10 and 25 mg dose arms; and

b) early discontinuation rates secondary to lack of efficacy were similar between the 10 and 25 mg dose arms.

To assess the sensitivity of the study results to patterns of early discontinuation of study medication, three analyses were performed (table 16). First, subjects in the placebo arm who discontinued therapy for lack of efficacy without meeting protocol-defined criteria were recategorized as responders,. Second, not only the placebo subjects who discontinued therapy for lack of efficacy but also those who had protocol violations or were lost to follow-up were similarly recategorized as successes. Finally, since there is some subjectivity to a subject's decision to request discontinuation due to lack of efficacy, this could be a source of bias. An analysis was carried out where all subjects who met protocol-defined criteria for lack of efficacy at any point in the study were recategorized as non-responders even if they later went on to have an ACR 20 response. All three analyses showed ENBREL to still be effective.

Table 16: Sensitivity analysis

	Placebo	10 mg	25 mg
Placebo LOE Discontinuations Not Meeting LOE Criteria Recategorized as Successes	24/80 (30%)	34/76 (45%)	48/78 (62%)
p value	p < 0.001 for 25 mg vs placebo		
Placebo LOE Discontinuations Not Meeting LOE Criteria and Other non-AE-related Discontinuations Recategorized as Successes	27/80 (34%)	34/76 (45%)	48/78 (62%)
p value	p < 0.001 for 25 mg vs placebo		
Patients Meeting LOE Criteria Recategorized as Failures	11/80 (14%)	24/76 (32%)	39/78 (50%)
p value	p < 0.007 for 25 mg vs placebo		

Functional assessment

Physical function was assessed using a version of the health assessment questionnaire (HAQ) which consists of a 6 page, patient- administered test of the effect on illness on function in daily life activities. It assessed:

- Degree of difficulty with performing life activities, e.g. dressing, eating, walking

- Need for help from another person for activities
- Change in physical limitations over 6 month timeframe
- Amount of pain, joint tenderness/swelling and their effect on activities and social function
- Overall health status, energy, happiness over the past 4 wks

The results indicate that disability scores were lower in the 10 mg and 25 mg treatment arms at month 3 and were lower still at month 6 (table 17). The improvement at months 3 and 6 in the ENBREL-treated groups was significantly greater than in the placebo-treated group.

Table 17: Disability Index derived from HAQ

Parameter	Placebo N = 80	TNFR:Fc 10 mg N = 76	TNFR:Fc 25 mg N = 78
Mean value[a]			
Baseline	1.7	1.7	1.6
Month 3	1.6	1.3	1.1
Month 6	1.7	1.2	1.0
Mean % change from BL			
Month 3	8%	30%*	36%*
Month 6	2%	34%*	39%*

a. Range: 0 = best assessment, 3 = worst assessment
* $p < 0.05$, each TNFR:Fc group vs. placebo
(p-value determined by ANOVA)

Quality of life

The SF-36 is a validated measure of quality of life in rheumatoid arthritis which includes eight subdomains: physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional and mental health. The SF-36 was assessed in only a fraction of subjects in the pivotal trial. However, the same questions from the vitality and mental health subdomains of the SF-36 are included in the HAQ utilized in this study and were thus assessed in all subjects. The results of the sponsor's analysis of the results of the vitality and mental health subdomains are presented tables 18 and 19. The results indicate that there was a significant improvement in the vitality and mental health subdomains of this quality of life measure.

Table 18: Vitality component of QOL

Parameter	Placebo N = 80	TNFR:Fc 10 mg N = 76	TNFR:Fc 25 mg N = 78
Mean value[a]			
Baseline	69	68	66
Month 3	64	53	48
Month 6	66	52	48
Mean % change from baseline			
Month 3	5%	19%*	26%*
Month 6	2%	22%*	25%*

a. Range: 1 = best assessment, 100 = worst assessment
* $p < 0.05$, each TNFR:Fc group vs. placebo
(p-value determined by ANOVA)

Table 19: Mental health component of QOL

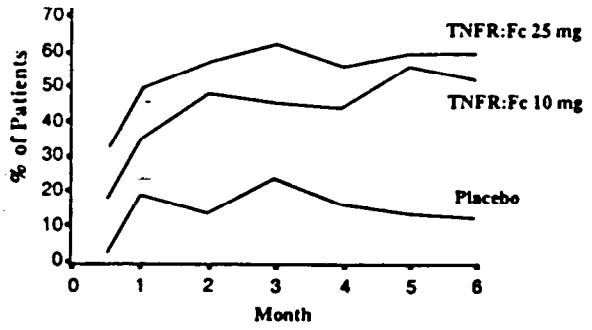
Parameter	Placebo N = 80	TNFR:Fc 10 mg N = 76	TNFR:Fc 25 mg N = 78
Mean value[a]			
Baseline	42	41	42
Month 3	39	32	30
Month 6	39	30	28
Mean % change from baseline			
Month 3	4%	11%*	29%*†
Month 6	3%	17%*	35%*†

a. Range: 1 = best assessment, 100 = worst assessment
* $p < 0.05$, each TNFR:Fc group vs. placebo
† $p < 0.05$; 10 mg TNFR:Fc vs. 25 mg TNFR:Fc
(p-value determined by ANOVA)

Assessment of durability of response

To determine the timecourse of the response seen with ENBREL, the proportion of subjects attaining an ACR 20 response was analyzed at different points during the trial. As shown in the figure and table below (table 20), an increased proportion of ACR 20 responders was observed in the ENBREL-treated arms as early as two weeks after beginning study medication and continued throughout the trial. In contrast, placebo responders were observed rarely before 4 weeks. The number of placebo responders peaked at 3 months and fell thereafter.

Table 20: Percent of Patients with 20% ACR Response



Time	Placebo N = 80	TNFR:Fc 10 mg N = 76	TNFR:Fc 25 mg N = 78
Week 2	1	17*	32*†
Month 1	18	34*	49*
Month 2	13	47*	56*
Month 3	23	45*	62*†
Month 4	15	43*	55*
Month 5	13	55*	59*
Month 6	11	51*	59*

* $p < 0.02$, vs. placebo
† $p < 0.04$, 10 mg vs. 25 mg
(p-value determined by likelihood chi-square test)

To evaluate the durability of responses for individual subjects participating in the trial, the proportion of subjects was assessed who attained a durable ACR 20 response, defined as a response which, once present, persisted continuously through month 6. As shown in table 21, an increased proportion of subjects in the ENBREL-treated arms attained a durable ACR 20 response. Durable ACR 20 responses were seen as early as 2 weeks in

the two treatment arms and additional durable responders were observed at the 1, 2 and 3 month assessments.

Table 21: Cumulative % of Patients Achieving an 20% ACR Response Persisting through Month 6

	Placebo	TNFR:Fc	
		10 mg*	25 mg*
Time	N = 80	N = 76	N = 78
Week 2	0	5	17
Month 1	4	20	31
Month 2	5	29	37
Month 3	5	30	44

*$p < 0.001$, each TNFR:Fc group vs. placebo
(p-values determined by log rank test)

Anti-ENBREL antibody formation

The formation of neutralizing antibodies to therapeutic agents may decrease the efficacy of these agents leading to losses of clinical responses over time. The sponsor developed [redacted] to detect anti-ENBREL antibodies. Using the less sensitive assay with a lower amount of antigen on the plates, the sponsor determined that 5 subjects tested positive for anti-ENBREL antibodies of 409 tested from the phase 2 and phase 3 RA trials. None of these were neutralizing antibodies. Some of the subjects with antibodies had a clinical response. Review of the data by the FDA revealed no subject who lost a clinical response upon development of anti-ENBREL antibodies. Results with a more sensitive [redacted] assay using a higher concentration of antigen demonstrated a 16% rate of positive antibodies among ENBREL-treated patients.

IV. OTHER EFFICACY TRIALS

The sponsor conducted two other randomized efficacy trials of ENBREL in patients with RA: a phase 2 trial and a methotrexate combination trial.

A. Phase 2 trial (16.0004)

Design

A phase 2 trial was designed as a 3 month double-blind, multicenter, dose escalation trial. 180 subjects with DMARD-failing RA were randomized to receive placebo or 0.25, 2, 16 mg/m^2 subcutaneously twice weekly. Inclusion criteria were similar to those of the phase 3 trial (16.0009) namely: failure of 1-4 DMARDs; at least 4 weeks off DMARDs prior to enrollment; active RA with at least 10 swollen and 12 tender/painful joints, either ESR of 28 or more or CRP exceeding 2.0 mg/dL or morning stiffness of 45 min or greater; stable prednisone no greater than 10 mg/d of prednisone or its equivalent. Subjects were excluded who had received an intra-articular corticosteroid injection within 4 wks of enrollment or with significant medical diseases. The prespecified endpoints of the trial were: swollen joint count, painful joint count, duration of morning stiffness, physician and patient global assessment, health assessment questionnaire (HAQ), pain score by VAS, ESR and CRP.

Efficacy

A statistically significant difference was seen in the percent change from baseline to day 85 for painful, swollen and total joint counts (no adjustments for multiple comparisons were made). For each measure, the greatest difference from baseline was seen in the subjects receiving the highest dose, i.e. 16 mg/m^2 followed by the 2 mg/m^2 dose. Significant differences were also seen in the HAQ and acute phase reactants (ESR and CRP). A dose-dependent increase in the proportion of subjects achieving an ACR20 response was observed as shown below (table 22).

Table 22: Efficacy results from phase 2 trial (16.0004)

	Placebo	TNFR:Fc		
		0.25 mg/m^2	2 mg/m^2	16 mg/m^2
	N = 44	N = 46	N = 46	N = 44
Time	n (%)	n (%)	n (%)	n (%)
ACR 20%				
Month 3	6 (14)	15 (33)	21 (46)	33 (75)

B. Methotrexate combination trial (16.0014)

Design

Trial 16.0014 was a double-blind, randomized, placebo-controlled multi-center trial of ENBREL 25 mg sc biw in 89 subjects with active RA receiving stable doses of MTX of 15-25 mg/wk. The inclusion criteria were similar to study 16.0009 except that subjects were to have been on oral or sc MTX for at least 6 mo with a stable MTX dose. A MTX dose of as low as 10 mg/wk was acceptable if the subject had a documented history of constitutional symptoms at higher doses. The criteria for disease activity were at least 6 swollen and 6 tender/painful joints. Subjects were randomized to receive placebo or ENBREL in a 1:2 ratio and treated for 6 months. Subjects continued to receive blinded study medication until all subjects had completed 6 months of therapy. Therefore some patients received more than 6 months of blinded therapy. The primary objective of the trial was originally to assess the safety of combination therapy, but during the trial, analysis of efficacy was added as an additional objective. Assessments were performed monthly during the trial. The primary efficacy endpoint was the ACR 20 at 6 mo. The ACR 20 at 3 months and the ACR 50 at 3 and 6 months were assessed as secondary efficacy endpoints.

Efficacy

The results of trial 16.0014 are presented in table 23. An increased proportion of subjects attained an ACR20 response at both three and six months in the ENBREL-treated group compared to those who received MTX alone. In addition, an increase in the proportion of subjects who achieved a more substantial ACR50 response was seen in the ENBREL-treated group, both at 3 months and at 6 months.

Table 23: Efficacy results of MTX combination trial (16.0014)

	Placebo/ MTX N=30 n (%)	TNFR:Fc /MTX N=59 n (%)
Primary endpoint		
20% ACR at month 6	8 (27)	42 (71)*
Secondary endpoints		
20% ACR at month 3	10 (33)	39 (66)**
50% ACR at month 3	0 (0)	25 (42)*
50% ACR at month 6	1 (3)	23 (39)*

* p<0.001, likelihood ratio, chi square test
**p=0.003, likelihood ratio, chi square test

Statistically significant improvements were seen for the ENBREL-treated group in the median scores on each of the components of the ACR 20 at 6 months (no adjustment was made for multiple comparisons). The degree of improvement in each parameter as reflected by a change in the median scores of the ENBREL-treated group (compared to placebo) was as follows: tender joints 70% improvement (28% with placebo); swollen joints 71% (37% in placebo); pain by VAS 68% (11% with placebo); physician global assessment 60% (27% with placebo); ESR 37% (21% with placebo); CRP 67% (24% with placebo). In addition, there was a 91% median decrease in the duration of morning stiffness compared to 20% with placebo. Last observation carried forward was utilized when data were missing.

Clinical responses were observed rapidly after initiation of ENBREL therapy. Thirty-nine percent of ENBREL-treated subjects had an ACR 20 at 1 week compared to 10% on placebo. At 1 month, 56% of ENBREL and 20% of placebo-treated subjects had attained an ACR 20 response. ACR 70 responses were observed in 15% (9/59) of ENBREL-treated subjects at 3 months and 6 months compared to none of the placebo subjects. The

responses appeared durable. Approximately 50% of ENBREL-treated subjects (compared to no placebo-treated subject) had attained an ACR 20 response at month 2 which persisted on each subsequent visit until the 6 month endpoint.

V. SAFETY ANALYSIS

A. Summary

Safety data are available from 1381 subjects treated with ENBREL of which 1039 had RA. Data from controlled trials indicate that treatment with ENBREL is associated with an increased incidence of injection site reactions and infections. Approximately 40% of treated subjects experienced injection site reactions which were all grade 1 and 2. The most common infection seen in the ENBREL-treated subjects was upper respiratory tract infection. Review of the entire safety database identified 19 cases of serious infection, including one death from staphylococcal septicemia. Although it cannot be determined with certainty that therapy with ENBREL is associated with an increased incidence of serious infections, reports of complicated, serious infections clearly raise concerns.

B. Size of safety database

At the time of submission of the Biologic Licensing Application, the sponsor submitted safety information on 849 subjects treated in 23 studies. With a safety update submitted on July 21, 1998, information is available on a total of 1381 individuals exposed to ENBREL of which 1039 subjects were patients with RA. A total of 733 RA subjects have received ENBREL for at least 6 months and 194 subjects for 12 months. The non-RA subjects exposed to ENBREL include 108 subjects treated in a trial of sepsis, normal volunteers treated in pharmacokinetic studies and investigator-sponsored INDs for various indications. Most of the summary information in this report will reflect information on the 531 RA patients reported in the original submission. When information is included which reflects the safety update, this will be stated specifically.

Table 24 summarizes the number of RA patients exposed to different doses of ENBREL and the periods of exposure.

Table 24: Study Drug Exposure in RA

Months	Low Dose (< 10 mg) n = 68 n (%)	Mid Dose (10 - < 25 mg) n = 110 n (%)	High Dose (≥ 25 mg) n = 294 n (%)	High Dose + Meth n = 59 n (%)	TNFR:Fc excl. Meth n=472 n (%)	All TNFR:Fc incl. Meth n=531 n (%)
<6	67 (99)	55 (50)	51 (17)	2 (3)	173 (37)	175 (33)
≥6	1 (1)	55 (50)	243 (83)	57 (97)	299 (63)	354 (67)
≥9	-	50 (45)	148 (50)	-	198 (42)	198 (37)
≥12	-	45 (41)	138 (47)	-	183 (39)	183 (34)
Total Patient Weeks (months) on Study Drug	697 (160)	3,239 (743)	11,850 (2,720)	1,362 (312)	15,787 (3,623)	17,148 (3,936)

Studies included: 16,0002, 16.0004, 16.0006C, 16.0008, 16.0009, 16.0009M, 16.0014, 16.0016, 16.0018, and 16.0019

C. Safety in non-RA studies

In a phase 2 study of patients with septic shock treated with single IV doses of ENBREL 0.15, 0.45 or 1.5 mg/kg, a dose dependent increase in 28 day mortality was observed. In the placebo group there were 10/33 deaths (30%) compared to 9/30 (30%) receiving the low dose of ENBREL, 14/29 (48%) receiving the middle dose and 26/49 receiving the high dose (53%). The deaths in the ENBREL-treated groups appeared to be due to sepsis.

D. Deaths and serious adverse events in RA studies

Four deaths occurred in the clinical trials. One ENBREL-treated subject and one subject who received placebo died of acute MI. One ENBREL-treated subject with ovarian ca died. As described below under **Serious Infections**, one ENBREL-treated subject died of staphylococcal sepsis. The deaths from acute MI were considered unrelated to study agent by the investigator.

In the pivotal trial, there were 5 instances in the placebo arm of SAEs, discontinuation secondary to an adverse event or grade 3 AEs compared to 8 instances in the 10 mg ENBREL arm and 5 in the 25 mg ENBREL arm (table 25).

Table 25: Deaths, SAE, Grade 3 or 4AEs and discontinuations for AE in phase 3 trial

Dose group (No. of pts.)	Pt. No.	SAE	Discontinuations due to AE/SAE	Grade 3 AEs	Grade 4 AEs	Deaths
Placebo (n = 5)		Disease progression	—	—	—	—
		—	Lung disorder (lung nodule)	—	—	—
		—	Headache	—	—	—
		Dehydration	—	—	—	—
		Bronchitis	Bronchitis (bacterial tracheitis)	—	—	—
10 mg (n = 8)		Cholecystitis, Dehydration	—	Cholecystitis Dehydration Pain (abdominal back)	—	—
		GI hem	—	GI hem	—	—
		—	Rash	—	—	—
		—	Leukopenia (Felty's syndrome)	—	—	—
		—	Hemoptysis (blood-tinged sputum)	—	—	—
		Myalgia Heart failure right	—	Dyspnea Heart failure right	—	—
		—	Headache (nonmigraine headache)	—	—	—
		—	ISR	—	—	—
25 mg		—	—	Bone disorder (ruptured disc)	—	—
(n = 5)		Cholelithiasis	—	—	—	—
		—	Pruritus (itching)	—	—	—
		Disease progression	—	—	—	—
		—	Hypotension	—	—	—

E. Malignancies in RA studies

Thirteen malignancies were identified in the safety database including the safety update. One of these occurred in a placebo-treated subject (cervical ca). Five of the 12 malignancies on ENBREL were basal cell carcinoma in subjects with prior histories of basal cell ca. The remaining 7 other cases were breast ca, adenocarcinoma of the lung, ovarian ca, ca of the prostate, adenoma of the common bile duct and Hodgkin's lymphoma. Additional information on these malignancies is provided in table 26.

Table 26: Malignancies

Patient identifier Age, gender	Diagnosis	Comments
5 subjects	basal cell ca	All w/ pre-existing basal cell ca
yo woman	breast ca	Had lumpectomy/LN dissection/XRT. Enrolled in extension study after 4 wks
yo woman	adenoca of lung	30 yr h/o smoking
yo woman.	Cervical ca	Received placebo/MTX in study 16.0014
yo woman	Ovarian ca	pelvic pain at week 12. Underwent surgery and chemo
yo man	ca of prostate	1 yr on drug. No evidence of mets
yo man	Adenoca of common bile duct	No mets
yo man	Hodgkin's lymphoma	25 mg, dx after 30 day off study
yo woman	ovarian ca	Received 25 mg dose

The incidence of malignancy observed with time since ENBREL exposure in depicted in table 27. No increase in the incidence of malignancy was observed with increased time of ENBREL exposure. The long term effect of ENBREL treatment on the incidence of malignancies is unknown.

Table 27: Incidence of Malignancies over time

	Months of ENBREL Treatment			
	0-6	6-12	12-18	>18
N	745	541	194	87
Cases	2	2	1	2
Types	Ovarian	Lung, bile duct	Hodgkin's	Prostate, breast

F. Infections in RA studies

The types of infections observed during the pivotal trial are shown in table 28. Upper respiratory infections (URIs) were increased in the ENBREL-treated subjects (29% and 33% in the 10 and 25 mg arms compared to 16% in controls). All the URIs were grade 1 and 2. Most subjects with URI experienced one or two episodes (table 29). After URIs, the most common infections in the ENBREL-treated groups were sinusitis, vaginitis, UTIs, bronchitis and flu syndrome.

Table 28: Infections in the pivotal trial

	Placebo	TNFR:Fc	
Event	N = 80 n (%)	10 mg N = 76 n (%)	25 mg N = 78 n (%)
None*	50 (63)	33 (43)	33 (42)
Any*	30 (38)	43 (57)	45 (58)
URI*	13 (16)	22 (29)	26 (33)
Sinusitis	9 (11)	8 (11)	9 (12)
Vaginitis	0	1 (1)	4 (5)
Cystitis	0	3 (4)	4 (5)
Bronchitis	3 (4)	2 (3)	3 (4)
Flu syndrome	4 (5)	7 (9)	3 (4)
Eye/conjunctivitis	1 (1)	3 (4)	2 (3)
Otitis	0	1 (1)	2 (3)
Pharyngitis	2 (3)	7 (9)	2 (3)
Skin infection	2 (3)	6 (8)	2 (3)
Abscess	0	0	1 (1)
Gastrointestinal	0	0	1 (1)
Gingival/dental	1 (1)	1 (1)	1 (1)
Herpes zoster	1 (1)	1 (1)	1 (1)
Pneumonia	0	0	1 (1)
Prostatitis	0	0	1 (1)
Salivary gland	0	1 (1)	1 (1)
Cellulitis	0	1 (1)	0
Rhinitis	0	1 (1)	0
Tracheitis	1 (1)	0	0
Urethritis	0	1 (1)	0

*$p < 0.05$ for a difference between the three groups determined by Fisher's exact test

Table 29: Frequency and Grade of URIs

	Placebo	TNFR:Fc	
		10 mg	25 mg
	N = 80	N = 76	N = 78
Parameter	n (%)	n (%)	n (%)
None	67 (84)	54 (71)$^{\Delta}$	52 (67)*
Any	13 (16)	22 (29)$^{\Delta}$	26 (33)*
1	10 (13)	21 (28)	18 (23)
2	2 (3)	1 (1)	7 (9)
3	1 (1)	0	1 (1)
Intensity			
Grade 1	12 (15)	20 (26)	25 (32)
Grade 2	1 (1)	2 (3)	1 (1)
Grade 3 or 4	0	0	0

Δ p = 0.08; 10 mg vs. placebo
* p = 0.016; 25 mg vs. placebo
(p-values determined by Fisher's exact test)

All of the infections observed in the 6 month pivotal trial were grade 1 or 2, as shown in table 30. Most subjects with infections experienced 1-3 infections during the trial.

Table 30: Frequency and Grade of Infection in the phase 3 trial

	Placebo	TNFR:Fc	
		10 mg	25 mg
	N = 80	N = 76	N = 78
Parameter	n (%)	n (%)	n (%)
1	21 (26)	26 (34)	26 (33)
2	7 (9)	12 (16)	11 (14)
3	1 (1)	2 (3)	6 (8)
4 - 6	1 (1)	3 (4)	0
7-9	0	0	1 (1)
10	0	0	1 (1)[a]
Intensity[a]			
Grade 1	21 (26)	36 (47)	41 (53)
Grade 2	9 (11)	7 (9)	4 (5)
Grade 3	0	0	0
Grade 4	0	0	0

a. 7 of 10 infections were recurrent vaginitis in patient 1315

Data from a 6 month trial may not fully reflect the infections seen with more extensive use. The complete safety database includes information on subjects treated in other trials of ENBREL with exposure of 194 subjects for greater than one year and 87 subjects for more than one and one-half years. Review of the entire safety database identified 19 serious infections in 17 subjects as shown in table 31. One case of staphylococcal septicemia resulted in death. Infections were deemed serious if they were associated with hospitalization and/or parenteral antibiotics. Comparable figures on serious infections in control subjects who did not receive ENBREL are unavailable because many of the events

occurred during long-term extension trials or during the maintenance phase of controlled trials.

Table 31: Serious Infections in all RA trials

Study	Subject #	Age, gender	Event	Reported grade in BLA	FDA grade	Comment
16.0002		female	Pyelonephritis	gr 3	gr 3	
16.0004		female	Bronchitis	gr 3	gr 3	
16.0008		female	Septic arthritis	gr 2	gr 3	See narrative
16.0008		male	Intra-abdominal abscess	gr 1	gr 3	Surgical complication, see narrative
16.0008		female	cellulitis	gr 2	gr 3	Complicated by osteomyelitis, see narrative
16.0018		female	osteomyelitis	gr 3	gr 3	same subject as listing above (# .0008)
16.0008		male	UTI	gr 3	gr 3	
16.0008		male	pneumonia	gr 3	gr 4	See narrative
16.0008		female	UTI	gr 3	gr 3	
16.0009		male	cellulitis of face	gr 3	gr 3	See narrative
16.00014		female	wound infection	gr 3	gr 3	See narrative
16.0018		female	pneumonia	gr 2	gr 2	2 day hospitalization
16.0018		male	septic arthritis	gr 3	gr 3	
16.0018		female	pneumonia	gr 3	gr 3	
16.0018		female	wound infection	gr 3	gr 3	Complication of corrective back surgery
16.0018		female	Foot abscess	gr 3	gr 3	Hospitalized for I&D
16.0018		female	Cellulitis of hand	N/A	gr 3	Hosp, IV antibiotics
16.0019		female	Post-op wound infection	gr 3	gr 3	Complication of arthroscopy for frozen shoulder
		female	staph sepsis	--	--	died, same subject as above listing (# .0019)

Narratives on some of these serious infections follow.

Staphylococcal sepsis resulting in death

—yo woman ' —— on ENBREL 25 mg biw for six months in controlled trial, then 6 mo in extension trial. Had left shoulder arthroscopy 10/97 complicated by staph wound infection. Concomitant meds: prednisone 10 mg, NSAIDS, anti-hypertensives. The week of July 16, presented to her primary care physician with increasing left knee pain and symptoms she felt were related to a flare-up of her RA. Her physician increased her prednisone dose from 5 mg bid to 20 mg bid. She was hospitalized 7/19/98 with hypoxia. Developed staph sepsis with septic arthritis of all prosthetic joints and rapid deterioration despite receiving IV vancomycin and nafcillin to which the staphylococcus was sensitive. Died 7/27. No source of infection identified. Portal of entry believed to be multiple excoriations from neurodermatitis.

Septic arthritis

— yo woman (subject— with RA since 1987 previously treated with corticosteroids, azathioprine, MTX, HQ and injectable gold began ENBREL 5/22/96. Concomitant meds include prednisone 5 mg/d and and NSAID. Dental extractions 11/26/96. Dentist suspected an infection and gave cephalexin. On 12/2/96, developed chills with pain in R knee, both wrists and L ankle. Arthrocentesis of knee was consistent with a septic arthritis although cultures were negative. She received IV cefuroxime and clindamycin and ceftriaxone until 12/28 when the infection resolved. She remained on study medication.

Intra-abdominal abscess

— yo man (subject — with RA since 1985 previously treated with oral corticosteroids, MTX and azathioprine. After 4 mo on study, underwent bowel reanastomosis for a colostomy on 10/23/96. After discharge, he was readmitted 10/31 with a localized abscess complicated by a fistula to the bladder. Treated with ampicillin/sulbactam and vancomycin. Study medication was discontinued from 10/31/96 to 11/7/96 then resumed. He underwent surgical closure of the colostomy and repair of the fistula on 1/14/97 without discontinuing study medication and had an uneventful recovery.

Cellulitis complicated by cutaneous ulcer and osteomyelitis

— yo woman (subject —, with RA since 1950 previously treated with ASA, NSAIDs, oral corticosteroids, azathioprine and MTX. Received ENBREL 25 mg biw from 7/16/96 through 7/29/97. Developed cellulitis on 7/12/97 at the site of trauma. Was treated with ceftraxone then cephelexin, cefazolin and ceftriaxone til 7/29/97, then amoxicillin. ENBREL was resumed on 8/1/97. Subject developed an ulcer at the infection site and osteomyelitis. Treated with ticarcillin/clavulanate from 8/22/97-10/8/97, then ciprofloxacin 9/5/97-10/15/97, then amoxicillin 10/15-10/18/97, then ciprofloxacin from

12/17/97-1/14/98. Infection resolved and the ulcer healed.

Pneumonia/ATN/diabetic hyperosmolar state

— yo man (—) with DM and RA since 1972 previously treated with D-pen, azathioprine, hydroxychloroquine, SSA, gold and CsA. Was treated with ENBREL 25 mg biw beginning 11/7/96. Developed bilateral pneumonia 1/9/97, admitted to ICU and treated with IV erythromycin and amoxicillin. Course was complicated by acute tubular necrosis, atrial fibrillation and diabetic hyperosmolar state. Five doses of ENBREL were missed during the hospitalization then treatment was resumed and continued til 10/6/97.

Cellulitis

— yo man (—) with RA since 1996 previously treated with oral corticosteroids, MTX, SSA, azathioprine, minocycline and hydroxychloroquine. Concomitant meds included an NSAID and prednisone. He began treatment with ENBREL 25 mg biw on 11/25/96. He had an abscessed tooth on 8/6/97 treated with pen V for 8 days. On 8/25/97, he developed staphylococcal cellulitis of the L cheek and was hospitalized from 8/25-28/97 and treated with ceftriaxone and ciprofloxacin. The infection did not resolve and required repeated courses of antibiotics. The infection resolved on 11/8/97.

Wound infection

Subject (—) received 25 mg ENBREL + MTX 15 mg po qw. After 1 mo on ENBREL, Study agent discontinued on 6/26/97 because of planned surgery for ventral hernia repair. Surgery was complicated by wound dehiscence and infection requiring two hospitalizations and surgical procedures.

The incidence of serious infections over time is presented in table 32. There was no evidence of an increasing incidence of infection with increasing duration of exposure within the timeframe of the studies:

Table 32: Serious Infections: Incidence over Time

	Months of ENBREL Treatment							
	< 3	**3-6**	**6-9**	**9-12**	**12-15**	**15-18**	**18-21**	**>21**
N	745	680	541	253	194	174	87	56
Cases	6	4	2	4	1	1	1	1
Incidence	0.8%	0.6%	0.4%	1.6%	0.5%	0.6%	1.1%	1.8%

ENBREL acts by inhibiting the action of tumor necrosis factor-α, a key mediator in immune responses against certain micro-organisms. Thus, it is possible that therapy with

ENBREL may impair host defense mechanisms during infections. The data from the six month controlled pivotal trial demonstrated an increased number of infections in ENBREL-treated subjects but no serious infections. The data from the uncontrolled extension trials showed some serious infections associated with longer term treatment. Whether these serious infections represent an increased incidence associated with ENBREL therapy or a background level cannot be determined with certainty from this uncontrolled data, but the reports of complicated, serious infections clearly raise concerns.

G. Injection site reactions, rashes and allergic reactions in RA studies

Injection site reactions were observed in approximately 40% of all ENBREL-treated subjects across several studies (tables 33 and 34). The injection site reactions were all of grade 1 (erythema only) and 2 (pain, swelling, pruritis or phlebitis). Rashes were observed in 7-20% of ENBREL-treated subjects with the higher frequencies in the higher dose arms. All but one were grade 1 and 2. Rash was a cause for patient discontinuation in five cases. There were 24 cases of adverse events which were possibly allergic including facial swelling, puffy eyes and hives. Two of these cases led to patient withdrawals and 22 continued treatment. None of the possibly allergic reactions were recurrent.

Table 33: Injection site reactions for all RA studies

	Placebo	TNFR:Fc				
	Placebo + Meth n = 154	Low Dose (<10mg) n = 68	Mid-Dose (10-<25mg) n = 110	High Dose (≥25mg) n = 294	TNFR:Fc + Meth n = 59	TNFR:Fc Excl. Meth. n = 472
ISRs number (%)*	15 (10)	15 (22)	46 (42)	137 (47)	25 (42)	198 (42)
Percent of ISRs of each intensity*						
Grade 1	8 (53)	9 (60)	18 (39)	50 (37)	5 (20)	77 (39)
Grade 2	7 (47)	6 (40)	28 (61)	87 (64)	20 (80)	121 (61)
Grade 3	0	0	0	0	0	0
Grade 4	0	0	0	0	0	0
No. of events/patient (mean)	0.2	1.0	3.2	4.3	3.2	3.5
No. of injections given/patient (mean)	32	21	60	81	47	67
No. of events/No. of injections	0.01	0.05	0.05	0.05	0.07	0.05
Event duration (mean) (days)	2.5	2.8	3.8	4.8	5.4	4.5

* Percent of ISRs seen.

Recurrent injection site reactions were not uncommon (table 34). Of the subjects who experienced injection site reactions in the 25 mg arm of the pivotal trial, 10 of the 38 had more than 10 reactions, 4 had 6-10 reactions and 24 had 1-5 reactions.

Table 34: Frequency and Grade of Injection Site Reactions in pivotal trial

	Placebo	TNFR:Fc	
		10 mg	25 mg
	N = 80	N = 76	N = 78
Parameter	n (%)	n (%)	n (%)
None	70 (88)	43 (57)*	40 (51)*
Any	10 (13)	33 (43)*	38 (49)*
1 - 5 ISR	9 (11)	26 (34)	24 (31)
6 - 10 ISR	1 (1)	3 (4)	4 (5)
> 10 ISR	0	4 (5)	10 (13)
Intensity[a]			
Grade 1	6 (8)	18 (24)	14 (18)
Grade 2	4 (5)	15 (20)	24 (31)

a. maximum intensity
* $p < 0.001$; each TNFR.Fc group vs. placebo
(p-values determined by Fisher's exact test)

H. Other adverse events in RA studies

Adverse event rates for the pivotal trial (16.0009) are presented in table 35. The figures given are crude event rates not corrected for the greater exposure time of subjects in the two active treatment arms arising from the fact that a larger proportion of the placebo-treated subjects discontinued early. The incidence of infection was higher in the ENBREL-treated subjects (57% of the 10 mg arm and 58% in the 25 mg arm) than in controls (38%) although dose-dependent effects were not seen. The incidence of injection site reaction (ISR) was also increased in the ENBREL-treated subjects: 43% and 49% in the 10 mg and 25 mg arms, respectively, compared to 13% in the placebo arm. The incidence of ISRs was slightly higher in the higher dose arm than the lower dose arm. The incidence of asthenia was higher in the active treatment arms (5% and 4% in the 10 mg and 25 mg arms) than in controls (0 of 80 subjects).

Table 35: Adverse Events of All Intensities occurring in ≥ 5% of Patients in Any Dose Group in Phase 3 trial

	Placebo	TNFR:Fc	
		10 mg	25 mg
	N = 80	N = 76	N = 78
Event	n (%)	n (%)	n (%)
Infection	30 (38)	43 (57)	45 (58)
Injection site reaction	10 (13)	33 (43)	38 (49)
Headache	8 (10)	15 (20)	11 (14)
Rhinitis	9 (11)	9 (12)	8 (10)
Accidental injury	4 (5)	1 (1)	7 (9)
Increased cough	1 (1)	2 (3)	7 (9)
Rash	3 (4)	6 (8)	6 (8)
Diarrhea	5 (6)	8 (11)	4 (5)
Nausea	7 (9)	6 (8)	4 (5)
Peripheral edema	3 (4)	1 (1)	4 (5)
Asthenia	0	4 (5)	3 (4)
Dizziness	2 (3)	5 (7)	1 (1)
Dyspepsia	1 (1)	5 (7)	1 (1)
Pain	3 (4)	6 (8)	1 (1)
Abdominal pain	3 (4)	4 (5)	0

I. Safety of methotrexate co-administration in RA studies

The safety of methotrexate (MTX) co-administration with ENBREL was assessed in a controlled trial comparing 59 subjects receiving MTX and ENBREL with 30 subjects receiving MTX alone (trial 16.0014, described above). In this six month trial, there were no deaths. Three serious adverse events were observed in each of the treatment arms. In the MTX alone arm: One subject developed cervical ca; One subject had an acute MI; One

subject had a GI bleed 2° to ulcer. In the MTX/ENBREL combination arm: One subject developed pancreatitis which was deemed idiopathic; Another subject had a wound infection which gave rise to 2 adverse event reports.

No increase in the overall rate of infections was observed in the combination treatment arm compared to the MTX only arm. In the ENBREL/MTX combination arm, 15 of 30 subjects (51%) had an infection compared to 37 of 59 subjects (63%) receiving MTX.

Although these data do not indicate a safety problem with ENBREL co-administration with MTX, definitive conclusions about the incidence of serious adverse events are difficult to reach because of the relatively small numbers of subjects studied.

J. Laboratory toxicities in RA studies

No pattern of laboratory abnormalities was observed consistently in the ENBREL-treated subjects in the pivotal trial (table 36). Three episodes of low lymphocyte counts, grade 3 were observed in the ENBREL 10 mg subjects but no cases were seen in subjects who received 25 mg.

Table 36: Grade 3 and 4 Laboratory Toxicities

			Placebo	TNFR:Fc	
				10 mg	25 mg
			N = 80	N = 76	N = 78
Parameter	Grade	Range	n (%)	n (%)	n (%)
ANC (low)	3	0.5 - 0.9 x 1000/cmm	0	1 (1)	0
	4	< 0.5 x 1000/cmm	0	1 (1)	0
Albumin (low)	4	2.5 - 2.0 gm/dL	1 (1)	0	0
Hemoglobin (low)	3	6.5 - 7.9 gm/dL	0	1 (1)	0
Lymphocytes (low)	3	< 0.5 x 1000/cmm	1 (1)	3 (4)	0
SGPT (high)	3	5.1 - 20.0 x ULN	0	0	1 (1)
WBC (low)	4	< 1.0 x 100/cmm	0	1 (1)	0

ULN = upper limit of normal

K. Autoantibody formation in RA studies

Measurements were made of anti-dsDNA, ANA, ACLA at baseline and at 3 and 6 months in the pivotal trial. The incidence of new positive ANA and anti-dsDNA by ELISA during the study compared to baseline was higher among ENBREL-treated patients than controls (tables 37 and 38). A similarly higher proportion of subjects became positive for anti-cardiolipin antibodies in the ENBREL-treated groups than in controls.

Table 37: New positive anti-dsDNA autoantibodies

	Placebo N = 79 n (%)	10 mg N = 77 n (%)	25 mg N = 77 n (%)
New pos anti-dsDNA	3 (4)	9 (12)	9 (12)
Positive anti-dsDNA	6 (8)	15 (19)	15 (19)

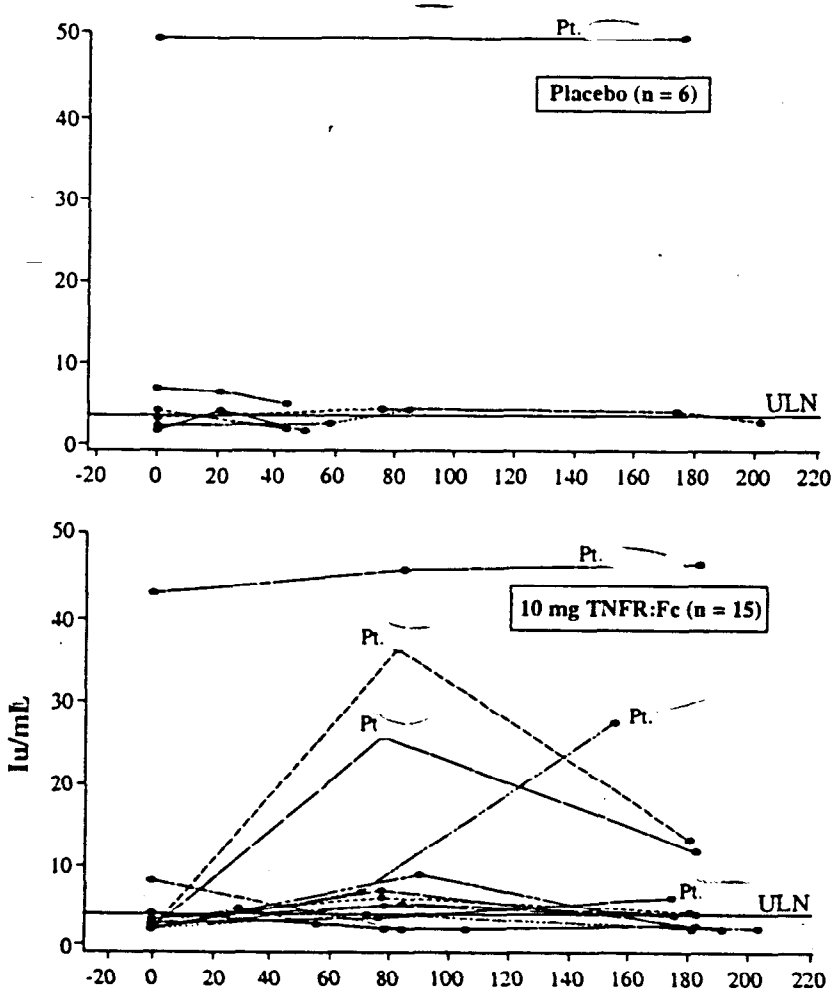
Table 38: New positive ANA autoantibodies

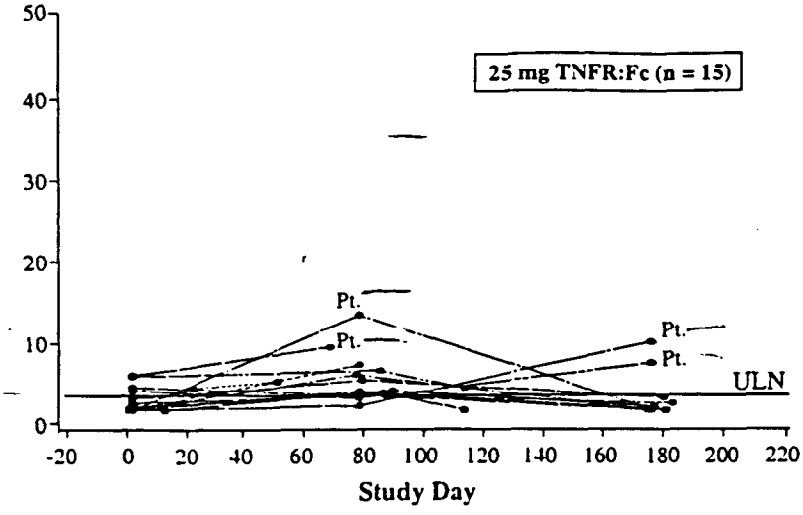
	Placebo N = 79 n (%)	10 mg N = 77 n (%)	25 mg N = 77 n (%)
New pos ANA	4 (5)	4 (5)	9 (12)
Positive ANA (≥1: 40)	22 (28)	32 (42)	27 (35)

When all subjects with elevated levels of autoantibodies at any time during the study are considered, six subjects in the placebo group had an elevated anti-dsDNA value during the study compared to 15 subjects each in the 10 and 25 mg ENBREL arms. The titers over time of subjects with one or more positive value in anti-dsDNA testing is shown in figure 2. There was marked variability of autoantibody levels in all groups. In addition to the above measurements, serum samples from the pivotal trial were also tested for anti-dsDNA antibodies using the crithidia luciliae assay. No placebo subjects were positive while 4/31 subjects in the 10 mg ENBREL arm and 3/33 in the 25 mg ENBREL arm were positive. One of the positive subjects in the 10 mg arm had a history of SLE and vasculitis. One of the positive subjects in the 25 mg arm developed a grade 1 neovascularization of the left disc which resolved in 30 days without treatment. None of the other subjects positive in the crithidia luciliae assay developed autoimmune features.

In conclusion, there was a higher incidence of new positive autoantibodies among ENBREL-treated subjects treated than controls. The titers were generally of low titer and there was no consistent pattern of rising titer with increased duration of exposure to ENBREL. No ENBREL-treated subject with autoantibodies developed symptoms of new autoimmune disease. Longer term follow-up will be required to assess the effect of longer duration of ENBREL exposure on the induction of autoimmune disease.

Figure 2: Patients with High Anti-dsDNA Levels





ULN = Upper limit of normal = 3.59 Iu/mL
Note: anti-dsDNA values > 50 Iu/mL graphed at 50 Iu/mL

Appendix 1: Study 16.0009, Allowed concomitant medications

- Corticosteroid dose not exceeding equivalent of 10 mg/d, stable for at least 4 weeks prior to screening evaluation
- NSAID not exceeding maximum dose recommended in the product insert, with dose stable for at least 4 weeks prior to screening
- Pain medications including: Tylenol #3®, Darvocet®, Percocet®, Lorcet®, and Tramadol®
- Intra-articular corticosteroids not allowed during trial or during the 4 weeks prior to the DMARD washout period

Appendix 2: ACR 20 response criteria

- 20% improvement in tender and swollen joint counts
- 20% improvement in three of the following measures: patient and physician globals, pain, disability, and an acute phase reactant

Appendix 3: PREDICTING RESPONSE WITH LOGISTIC REGRESSION AT VISIT #12

The LOGISTIC Procedure
Analysis of Maximum Likelihood Estimates

Variable	DF	Parameter Estimate	Standard Error	Wald Chi-Square	Pr > Chi-Square	Standardized Estimate
INTERCP1	1	-0.3239	0.4361	0.5516	0.4577	.
INTERCP2	1	0.9072	0.4421	4.2107	0.0402	.
INTERCP3	1	1.9605	0.4704	17.3716	0.0001	.
BLHAQ	1	0.6071	0.2457	6.1048	0.0135	0.215138
BLJTPNCT	1	-0.0307	0.0121	6.4898	0.0108	-0.267127
BLJTSWCT	1	0.0259	0.0150	2.9891	0.0838	0.173920
PLACEBO	1	1.0144	0.3539	8.2163	0.0042	0.265574
HIGH	1	-0.9267	0.3096	8.9621	0.0028	-0.241104

Conditional Odds Ratios and 95% Confidence Intervals

Variable	Variable Label	Wald Confidence Limits Odds Ratio	Lower Limit	Upper Limit
INTERCP1	Intercept 0			
INTERCP2	Intercept 1			
INTERCP3	Intercept 2			
BLHAQ	Baseline HAQ - Disability Index	1.835	1.134	2.970
BLJTPNCT	Baseline Tender (Painful) Joint Count	0.970	0.947	0.993
BLJTSWCT	Baseline Swollen Joint Count	1.026	0.997	1.057
PLACEBO	PLACEBO=1, OTHER=0	2.758	1.378	5.518
HIGH	25 MG=1, OTHER=0	0.396	0.216	0.726